09914270 .092401

JC20 Rec'd PCT/PTO 24 AUG 2001

FORM PTO-1390 (Modified) (REV 5-93) U.S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		016915-0244
		U.S. APPLICATION NO (If known, see 37 C.F.R. 1.5) Unassigned 09/914270
INTERNATIONAL APPLICATION NO. PCT/EP00/00323	INTERNATIONAL FILING DATE January 17, 2000	PRIORITY DATE CLAIMED February 24, 1999

TITLE OF INVENTION
USE OF R-ARYL PROPIONIC ACIDS FOR PRODUCING MEDICAMENTS TO TREAT DISEASES IN HUMANS AND ANIMALS, WHEREBY SAID DISEASES CAN BE THERAPEUTICALLY INFLUENCED BY INHIBITING THE ACTIVATION OF NF-κB

APPLICANT(S) FOR DO/EO/US
Gerd GEISSLINGER and Kay BRUNE

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   - ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   - ☒ has been transmitted by the International Bureau.
   - ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   - ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   - ☐ have been transmitted by the International Bureau.
   - ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   - ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☒ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).
11. ☒ Applicant claims small entity status under 37 CFR 1.27 .

Items 12. to 17. below concern other document(s) or information included:

12. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
13. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
14. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☒ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ Other items or information:

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
Unassigned 09/914270	PCT/EP00/00323	016915-0244

18. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5): Search Report has been prepared by the EPO or JPO.....$860.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482).....$690.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2).....$710.00		
Neither international preliminary examination fee (37 CFR 1.482) nor International search fee (37 CFR 1.445(a)(2)) paid to USPTO..... $1,000.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4).....$100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$860.00	
Surcharge of $130.00 for furnishing the oath or declaration later than 20 Months from the earliest claimed priority date (37 CFR 1.492(e))	$130.00	

Claims	Number Filed		Included in Basic Fee		Extra Claims		Rate		
Total Claims	10	-	20	=	0	×	$18.00	$0.00	
Independent Claims	2	-	3	=	0	×	$80.00	$0.00	
Multiple dependent claim(s) (if applicable)							$270.00		
TOTAL OF ABOVE CALCULATIONS =								$990.00	
Reduction by ½ for filing by small entity, if applicable.								$495.00	
SUBTOTAL =								$495.00	
Processing fee of $130.00 for furnishing English translation later the 20 months from the earliest claimed priority date (37 CFR 1.492(f). +									
TOTAL NATIONAL FEE =								$495.00	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +									
TOTAL FEES ENCLOSED =								$495.00	
							Amount to be: refunded	$	
							charged	$	

a. ☒ A check in the amount of $495.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 19-0741 in the amount of $0.00 to the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0741. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Foley & Lardner
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109

SIGNATURE

NAME RICHARD L. SCHWAAB

REGISTRATION NUMBER 25,479

Applicant or Patentee: Gerd GEISSLINGER et al.
Serial or Patent No.: PCT/EP00/00323 Atty. Dkt. No. 016915/0244
Filed or Issued: January 17, 2000
For: USE OF R-ARYL PROPIONIC ACIDS FOR PRODUCING MEDICAMENTS TO TREAT DISEASES IN HUMANS AND ANIMALS, WHEREBY SAID DISEASES CAN BE THERAPEUTICALLY INFLUENCED BY INHIBITING THE ACTIVATION OF NF-κB

VERIFIED STATEMENT (DECLARATION) CLAIMING SMALL ENTITY STATUS
(37 CFR 1.27) — SMALL BUSINESS CONCERN

I hereby declare that I am

( ) the owner of the small business concern identified below:
( ) an official of the small business concern empowered to act on behalf of the concern identified below:

NAME OF CONCERN: PAZ ARZNEIMITTEL-ENTWICKLUNGSGESELLSCHAFT MBH

ADDRESS OF CONCERN: In der Schildwacht 13, D-65933 Frankfurt am Main
Federal Republic of Germany

I hereby declare that the above-identified small business concern qualifies as a small business concern as defined in 13 CFR 121.3-18 and reproduced in 37 CFR 1.27, for purposes of paying reduced fees under section 41(a) and (b) of Title 35, United States Code, in that the number of employees of the concern, including those of its affiliates, does not exceed 500 persons. For purposes of this statement, (1) the number of employees of the business concern is the average over the previous fiscal year of the concern of the persons employed on a full-time, part-time or temporary basis during each of the pay periods of the fiscal year, and (2) concerns are affiliates of each other when either, directly or indirectly, one concern controls or has the power to control the other, or a third party or parties controls or has the power to control both.

I hereby declare that rights under contract or law have been conveyed to and remain with the small business concern identified above with regard to the invention, entitled USE OF R-ARYL PROPIONIC ACIDS FOR PRODUCING MEDICAMENTS TO TREAT DISEASES IN HUMANS AND ANIMALS, WHEREBY SAID DISEASES CAN BE THERAPEUTICALLY INFLUENCED BY INHIBITING THE ACTIVATION OF NF-κB by inventor(s) Gerd GEISSLINGER and Kay BRUNE described in

( ) the specification filed herewith
(X) application serial no. PCT/EP00/00323, filed January 17, 2000
( ) patent no._____ , issued _____

If the rights held by the above-identified small business concern are not exclusive, each individual, concern or organization having rights to the invention is listed below* and no rights to the invention are held by any person, other than the inventor, who would not qualify as an independent inventor under 37 CFR 1.27(a)(1) if that person made the invention, or by any concern which would not qualify as a small business concern under 37 CFR 1.27(a)(2) or a nonprofit organization under 37 CFR 1.27(a)(3). * NOTE: Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities: (37 CFR 1.27)

NAME: _____
ADDRESS: _____
( ) INDIVIDUAL( ) SMALL BUSINESS CONCERN( ) NONPROFIT CORPORATION

NAME: _____
ADDRESS: _____
( ) INDIVIDUAL( ) SMALL BUSINESS CONCERN( ) NONPROFIT CORPORATION

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate: (37 CFR 1.27.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

NAME OF PERSON SIGNING: Dr. Otto Schuster
TITLE OF PERSON OTHER THAN OWNER: _____
ADDRESS OF PERSON SIGNING: D-65812 Bad Soden, Kelkheimer Str. 69, Germany
SIGNATURE: _____ DATE: 29/08/01

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No. 016915-0244

In re patent application of

Gerd GEISSLINGER et al.

Serial No. Unassigned

Filed: August 24, 2001

For: USE OF R-ARYL PROPIONIC ACIDS FOR PRODUCING MEDICAMENTS TO TREAT DISEASES IN HUMANS AND ANIMALS, WHEREBY SAID DISEASES CAN BE THERAPEUTICALLY INFLUENCED BY INHIBITING THE ACTIVATION OF NF-κB

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination of the above-identified application, Applicant respectfully request that the following amendment be entered into the application:

IN THE SPECIFICATION:

Please replace the specification as filed internationally with the attached annex specification issued with the International Preliminary Examination Report for the same application.

IN THE TITLE:

Please amend the title to read the following:

USE OF R-ARYL PROPIONIC ACIDS FOR PRODUCING MEDICAMENTS TO TREAT DISEASES IN HUMANS AND ANIMALS, WHEREBY SAID DISEASES CAN BE THERAPEUTICALLY INFLUENCED BY INHIBITING THE ACTIVATION OF NF-κB

IN THE CLAIMS:

Please delete claims 1 through 10 and add new claims 11 through 20 as follows:

--11. Use of the R-enantiomers of arylpropionic acids or their derivatives for the preparation of medicaments which inhibit the NF-κB activation cascade and therefore are suited to the treatment of diseases which may be influenced therapeutically beneficial by the inhibition of NF-κB production.

12. Use according to claim 11, wherein the medicament contains the R-arylpropionic acid in an amount of 50 to 1000 mg/dose.

13. Use according to claim 11, wherein the R-arylpropionic acid or R-arylpropionic acid derivative is essentially free of S-arylpropionic acids or S-arylpropionic acid derivatives.

14. Use according to claim 11, wherein the R-arylpropionic acids are selected from those not metabolising to CoA thioesters, and especially are selected from R-flurbiprofen, R-ketoprofen, R-naproxen, R-tiaprofenic acid, and/or R-fenoprofen.

15. Use according to claim 11, wherein the active material is present as alkali metal, alkaline earth metal, ammonium, amino acid salt, preferably as lysinate, megluminate, trometamine, arginate or aluminium salt.

16. Use according to claim 11, wherein the medicament contains usual adjuvants and carrier materials.

17. Use according to claim 11, wherein the medicaments are produced in the form of tablets, dragees or other orally usable forms.

18. Use according to claim 11, wherein the active materials are used in rapidly inflowing, retardedly inflowing or combined in rapidly and retardedly inflowing form.

19. Use according to claim 11, wherein they are used for the therapy of rheumatic diseases, pain, asthma, tumours, immune diseases, shock, inflammatory intestinal diseases (crohn's disease, colitis ulcerosa), radiation damages, arteriosclerosis and rejection reactions after tissue and organ transplantation.

20. Mixtures containing 50-1000 mg R-enantiomer and 50-300 mg S-enantiomer in one dosage form in a ratio in which the inhibition of the NF-κM activation by the R-enantiomer and the inhibition of COX by the S-enantiomer are adapted in activity and period of action to the respective indication.--

REMARKS

Entry of the foregoing amendments prior to examination is respectfully requested.

Respectfully submitted,

34371

August 24, 2001
Date

Richard L. Schwaab
Registration No. 25,479

FOLEY & LARDNER
3000 K Street, N.W. Suite 500
Washington, D.C. 20007-5109
(202) 672-5300

Patent Claims

1. Use of R-enantiomers of arylpropionic acids or arylpropionic acid derivatives for the preparation of medicaments which inhibit the NF-κB activation cascade and thus are suitable for the treatment of diseases which can be therapeutically positively influenced by the inhibition of NF-κB formation.

2. Use according to claim 1, characterised in that the agent contains the R-arylpropionic acid in an amount of 50 to 1000 mg/dose.

3. Use according to claim 1 or 2, characterised in that the R-arylpropionic acid or R-arylpropionic acid derivatives are substantially free of S-arylpropionic acid or S-arylpropionic acid derivatives.

4. Use according to claim 1 to 3, characterised in that, as R-arylpropionic acids, there are used acids not metabolising to CoA thioesters, especially R-flurbiprofen, R-ketoprofen, R-naproxen, R-tiaprofenic acid or R-fenoprofen.

5. Use according to claim 1 to 3, characterised in that the active material is present as alkali metal, alkaline earth metal, ammonium, amino acid salt, preferably lysinate, megluminate, trometamine, arginate or aluminium salt.

6. Use according to claim 1 to 4, characterised in that the medicament contains usual adjuvant and carrier materials.

English Translation of Annex to International Preliminary Examination Report

New pages filed 10.10.2000

Use of R-arylpropionic acids for the production of medicaments for the treatment of diseases in humans and animals which can be therapeutically influenced by the inhibition of the activation of NF-κB.

The subject of the present invention is the use of R-arylpropionic acids for the production of medicaments for the treatment of diseases in humans and animals which can be therapeutically influenced by the inhibition of the activation of NF-κB.

Arylpropionic acids and their derivatives have long since been used as nonsteroidal anti-inflammatory and analgesically effective medicaments. Known representatives of the active material group are ibuprofen, flurbiprofen, ketoprofen, napoxen, tiaprofenic acid and fenoprofen /propionic acid derivatives: Goodman and Gilman's, The pharmacological basis of therapeutics, Chapter 27, p. 637 (ninth edition, 1996/7.

On the basis of the molecular structure with an asymmetrical C-atom, arylpropionic acids and their derivatives are chiral, thus occur as R- and S-enantiomeric forms. In the case of the chemical synthesis, these active materials normally occur as racemate. Apart from S-naproxen /Williams: Enantiomers in arthritic disorders; Pharmac. Ther., Vol. 26, pp. 273-295 (1990); Evans: Enantioselective pharmacodynamics and pharmacokinetics of chiral non-steroidal anti-inflammatory drugs, Eur. J. Pharmacol., 42, 237-256 (1992/7 and recently dexibuprofen

/Symposium: Update on S(+)-ibuprofen; Going /Kitzbühl, 2 to 4 February, 1996/7 and dexketoprofen /Scrip No. 1831, June 22nd 1993, p. 7, Scrip No. 2144, July 9th 1996, p. 16/7, these active materials have hitherto been used as racemates.

The therapeutically desired inflammation-inhibiting and pain ameliorating action of arylpropionic acuds and their derivatives is essentially ascribed to the inhibition of the prostaglandin biosynthesis /Vane and Botting: Overview - mechanism of action of anti-inflammatory drugs. In: Improved non-steroidal anti-inflammatory drugs - COX-2 enzyme inhibitors, p. 1 - 27, Lancester - Kluwer Academic Publishers (1996)7. This takes place via the inhibition of the enzymes cyclooxygenases 1 and 2 (COX-1 and COX-2 or PGHS-1 and PGHS-2) participating in the formation of prostaglandins. Due to the reduced formation of prostaglandins, the inflammation symptoms, such as pain, swelling, reddening, oedema formation, heating and function limitation, the inflammation symptoms standing in conjunction with these inflammation mediators are weakened. The inhibition of the prostaglandin biosynthesis is taken as general characteristic of the mechanism of the anti-inflammatory and of the analgesic action. The therapeutically desired inhibition of the prostaglandin production in the diseased object tissue leads in other organ systems, which indicate the presence of certain prostaglandin concentrations, to undesired

medicament actions. Especially affected by the undesired actions are the stomach-intestine tract, the kidneys, the lungs and the blood platelets.

It is known that, with reference to the prostaglandin synthesis inhibition, substantial differences exist between the enantiomeric forms of the arylpropionic acids /Williams (v. supra); Evans (v. supra); Brooks and Day: New nonsteroidal anti-inflammatory drugs, Birkhauser Verlag, Basel, p. 119-126 (1985)7. Whereas all S-enantiomers of these substances show an outstanding prostaglandin synthesis inhibition, in the case of the R-enantiomers this is not found in the therapeutically relevant concentration range. Consequently, in therapeutic concentrations, to the R-arylpropionic acids and their derivatives are ascribed neither the desired nor the undesired medicinal actions which stand in conjunction with the inhibition of the prostaglandin production. Independently of the absence of these action mechanism-specific undesired actions, the R-enantiomers of this active material class display substance-specific undesired actions.

Because of the hitherto therapeutic and economic importance of the arylpropionic acids used as racemate, it is sought to establish the reasonableness of the use of racemic active materials. In the case of ibuprofen, the use of the racemate is essentially based on the fact that, in the human or animal organism, a more or less marked inversion of R-isoprofen to S-ibuprofen takes

place /Caldwell et al., The metabolic chiral inversion and dispositional enantioselectivity of the 2-aryl-propionic acids and their biological consequences; Biochemical Pharmacology, Vol. 37, No. 1, pp. 105-114 (1988)/ so that also a part of the R-form, after inversion to the S-form, can be effective as prostaglandin synthesis inhibitor. Furthermore, for R-ibuprofen, an inhibition of the polymorphonuclear leukocytes in vitro is described which could prove to be advantageous in the case of inflammatory diseases /Villanueva et al., Equipotent inhibition by R(-)-, S(+)- and racemic ibuprofen of human polymorphonuclear cell function in vitro; Br. J. Pharmac., 35, 235-242 (1993)/. However, the therapeutic relevance of this mechanism in the case of use of racemic iboprofen could not be shown. For R-flurbiprofen, the inversion can be neglected.

The fact that the therapeutic action of the aryl-propionic acids is essentially ascribed to the prostaglandin synthesis inhibition has led to the recognition that the use of the pure S-enantiomers, possibly of the racemic compounds but not of the pure R-enantiomers is meaningful. First with the surprising discovery that R-flurbiprofen displays an antinociceptive effect whidh does not stand in connection with the inhibition of the peripheral prostaglandin biosynthesis was the development of medicaments based on R-flurbiprofen /DE 40 28 906 C2; EP 0 607 128 B1; USA 5,206,029 and

5,200,1987 as analgesic without inflammation-inhibiting active component initiated. Later, a pain-ameliorating action was also described for R-ketoprofen /DE 43 19 438 C1; WO 93/17667/.

Recent publications confirm the antinociceptive effect of R-flurbiprofen /Geisslinger, Schaible: New insights into the site and mode of antinociceptive action of flubiprofen enantiomers, J. Clin. Pharmacol., 36, 513-520 (1996), Buritova, Besson, Peripheral and/or central effects of racemic, S(+)- and R(-)-flurbiprofen on inflammatory nociceptive processes: a c-Fos protein study in the rat spinal cord; British J. Pharmacology, 125, 87-101 (1998)/. In clinical studies on patients, the pain-ameliorating action of R-flurbiprofen /Fig. 1/ and R-ketoprofen /Cooper et al., Analgesic efficacy and safety of R-ketoprofen in postoperative dental pain; J. Clin. Pharmacol., 38, 11S-18S (1998)/ could be demonstrated.

Fig. 1 Placebo-controlled double blind study on 180 women with acute post-episiotomy pain (average value curves)

The hospitalised pateints were randomised in three medication groups each with 50 patients and a placebo group (30 patients). Within 48 hours, each patient received, after otherwise normally proceeding delivery, a single dose of the study medication to be investigated (25 mg R(-)-flurbiprofen or 100 mg (R)-flurbiprofen or

1000 mg paracetamol) or a placebo, administered orally. Shortly before the oral administration of the test preparation or of the placebo and at precisely fixed investigation point of time (15, 30, 45, 60, 120, 180, 240, 300 and 360 minutes), the patients were questioned with regard to their feeling of pain. The effectiveness of the individual preparations were assessed on the basis of a pain feeling scale (0 = none, 1 = mild, 2 = moderate, 3 = strong). The time courses are summarised in the average value curves of the individual patients given in Figure 1.

Animal experimental studies verify that the action of R-flurbiprofen can be explained via the inflammation-inhibiting and antinociceptive action on the central nervous system /Buritova (v. supra); Neugebauer et al., Antinociceptive effects of R(-)- and S(+)— flurbiprofen on rat spinal dorsal horn neurons rendered hyper-excitable by an acute knee joint inflammation; J. Pharmacol. Exp. Ther; 275, 618-628 (1995)7. The known peripheral inflammation-inhibiting and antinociceptive action of flurbiprofen could, on the other hand, be found exclusively in the case of the S-enantiomers /Buritova (v. supra) and Neugebauer (v. supra)7. According to the present state of knowledge, there results therefrom the significant consequence that, for the optimal treatment of the peripheral inflammatory diseases, S-arylpropionic acids are to be used as agents of choice. For the reduction of the undesired activities on the stomach-

intestinal tract etc. connectedwith the prostaglandin synthesis inhibition, e.g. S-flurbiprofen should not be taken orally but rather administered locally to the inflammed or painful place. However, because of the central action, R-flurbiprofen should be administered systemically /Buritova (v. supra)/, e.g. orally, intramuscularly or intravenously.

Contrary to this newest knowledge for the practically exclusive central action of R-flurbiprofen, it was now surprisingly found that R-flurbiprofen in certain concentrations is a potent and specific inhibitor of the activation of the nuclear transcription factor NF-κB. NF-κB is a ubiquitous transcription factor which takes up a central role in cells in the case of immune and inflammation reactions, as well as in the expression of cytokines, chemokines, cell adhesion molecules, growth factors, immune receptors, acute phase proteins , diverse enzymes and other transcription factors /Lee, Burckart: Nuclear factor kappa B: Important transcription factor and therapeutic target, J. Clin. Pharm., 38, 981-993 (1998)/.

The NF-κB activation can be inhibited by various active materials at different steps of the activation cascade. Thus, glucocorticoids inhibit NF-κB by direct association or by strengthening of the expression. Cyclosporins and tacrolimus prevent the NF-κB activation by inhibition of the calcineurin action of the phosphatases

which indirectly induce the I-κB decomposition. Deoxyspargualin inhibits NF-κB by blockade of its nucleus displacement. Aspirin and salicylates inhibit present occurances which induce the I-κB phosphorylation. Tepoxalin and antioxidants inhibit the NF-κB activation by changing of the redox state of the cell. Further researches are necessary in order to develop specific inhibitors of the treatment of diseases which are influenced by NF-κB /Lee, Burckart: Nuclear factor kappa B; Important transcription factor and therapeutic target, J. Clin. Pharm., 38, 981-992 (1998)/.

It is known that R-ibuprofen and S-ibuprofen inhibit the activation of the transcriptuon factor NF-κB by phorbol esters (TPA), which is attributed to a regulation of the protein kinase C (PKC) activated by phorbol esters and thereby brought about phosphorylation and inactivation of the I-κB but is not able to influence an NF-κB activation by PGE_2 or lipopolysaccharides (LPS). The usability of ibuprofen is, therefore, limited /N. Scheuren et al., "modulation of transcription factors by nonsteroidal anti-inflammatory drugs", Naunyn-Schmiedeberg's Arch. Pharmacol., Vol. 354, No. 4, suppl. 1, 1996; N. Scheuren et al., "Enantiomers of the nonsteroidal anti-inflammatory drug ibuprofen are potent and specific inhibitors of transcription factor NF-kappa, beta, "Naunyn-Schmiederberg's Arch. Pharmacol., Vol. 357, No. 4 suppl., 1998; N. Schueren et al. "Modulation of transcription factor NF-kappa,beta

by enantiomers of the nonsteroidal drug ibuprofen, Br. J. Pharmacol., Vol. 123, No. 4, 1998; N. Scheuren et al., "Weak inhibitors of cyclooxygenases may exert their antinociceptive effects by modulation of transcription factors, Adv. Exp. Med. Biol., Vol. 433, 1997.

The invention has now set itself the task to find further active materials which inhibit NF-κB activation.

Surprisingly, it has now been found that other non-racemising R-arylpropionic acids can intervene via the specific inhibition of steps within the NF-κB cascade in the disease happenings. Because of the ubiquitous function of the transcription factor NF-κB in the case of the gene regulation, medicaments with N-arylpropionic acids or their derivatives are suitable not only for the known pain amelioration via the antinociceptive action on the central nervous system /DE 40 28 906 C2/ but, in the case of suitable use and dosage, can also be used in the case of all diseases in which an inhibition of the NF-κB can be therapeutically advantageously used. According to the invention, these medicaments can be used not only in the case of pain and rheumatism but also in the case of immune diseases, asthma, shock, inflammatory intestinal diseases (Crohn's disease, colitis ulcerosa), radiation damages, arteriosclerosis, in the treatment of rejection reactions after tissue and organ transplants etc., in each case in appropriate doses and pharmaceutical formulations.

The here reported observation of the inhibition of the NF-κB formation is surprising because, according to the prior art, the pharmacological effects of the arylpropionic acids were ascribed to other mechanisms. This has hitherto led to the use of the racemates or of the S-enantiomers in comparatively small doses in the case of pains and inflammations.

Furthermore, in WO 98/09603 is described the usability of R-NSAID's in neoplastic diseases, especially colon and breast cancer, cystic fibrosis and Alzheimer's disease.

Surprisingly, it has now been found that R-flurbiprofen and other R-arylpropionic acids not metabolising to CoA-thioesters and thus racemising inhibit the NF-κB activation about 100 times more potently than the corresponding S-enantiomers. However, in order to achieve a sufficient action, they must be used in higher dosages than are usual in the case of the known therapeutic use of racemic arylpropionic acids. However, because of the good compatability on the basis of the practically absent action of these R-arylpropionic acid dosages on the peripheral prostaglandin biosynthesis and the racemising to the S-enantiomers not taking place, it is possible, in the case of use of the R-enantiomers, to make the dose so high that the desired inhibiting action on the NF-κB activation is achieved without having to fear the undesired actions

brought about by the S-form. The active materials are, therefore, preferably used substantially free of the S-enantiomers, i.e. with an optical purity of over 90%, especially over 99%, if, as "side effect", the known pain- and inflammation-inhibiting action of the S-enantiomers is also not desired. In contradistinction to R-ibuprofen, in this regard undesired actions because of the absent R ⟹ S inversion in the case of the R-arylpropionic acids not metabolising to the CoA thioesters are not to be expected. Thus, the medicaments according to the invention permit an improved therapeutic breadth to be expected in comparison with the use of the racemic arylpropionic acids or of their S-enantiomers, The investigations carried out on humans verify the good gastrointestinal compatibility of R-flurbiprofen and other R-arylpropionic acids /Jerussi et al., Clinical endoscopic evaluation of the gastroduodenal tolerance to ketoprofen, flurbiprofen, racemic ketoprofen and paracetamol: A randomised, single-blind, placebo-controlled trial; J, Clin. Pharmacol., 38, 19S-24S (1998)/, which has been indicated in previously carried out animal experiments /DE 40 28 906 C2/.

Since the discovery of the nuclear transcription factor NF-κB before about one decade, extensive research works have been carried for the biological function and ffor the influencing of the NF-κB formation by endogenic and exogenic substances. Of the known pharmacological substances, hitherto inter alia glucocorticoids, such as

dexamethasone and prednisone, immune suppressives, such as cyclosporin, tacrolimus and deoxyspergualin in therapeutic concentrations have been described as effective on the NF-κB activation. For the metabolites intermediately formed in the case of the biochemical inversion of R-ibuprofen to S-ibuprofen, an inhibition of the NF-κB activation was also demonstrated for an R-ibuprofen coenzyme A thioester and speculatively assumed that also R-ibuprofen, via the known metabolic activation in the human body to the R-ibuprofen-CoA thioester, would show an action which R-ibuprofen itself does not possess. /Brune et al., Medicament containing ibuprofen thioester as inhibitor of the Nf-κB-dependent formation of mediators of inflammations and pain, DE 197 16 713 A1, WO 98/47502/7.

Surprisingly, it has now been found that other therapeutically used arylpropionic acid derivatives, such as flurbiprofen, ketoprofen, naproxan, tiaprofenic acid and fenoprofen, which display no noteworthy formation of CoA-thioesters in humans and, therefore, not racemising bring about an outstanding inhibition of the activation of NF-κB and thus possess the potential for the therapeutic effects associated with the influencing of this mechanism. In the following, this group is designated with "not racemising (abbreviated n.r.) R-arylpropionic acids".

The medicaments according to the invention based on n.r. R-arylpropionic acids and their derivatives as inhibitors of the NF-κB activation for the therapy of diseases which are influenced by the modification of the NF-κB activation are based on the following experimental investigations:

Fig. 2: Concentration-dependent influence of R- and S-flurbiprofen on the activation of the transcription factor NF-κB in RAW cells. The gel retention analysis (electromobility shift assay: DIG gel shift kit, Boehminger Mannheim) shows that LPS (1 µg/ml) leads to an activation of NF-κB (p50/p65 complex of NF-κB (trace No. 2 and 10). Macromolar concentrations of R-flurbiprofen (trace No. 3,4,5,6, 7 against trace No. 2 as control) were in the position to inhibit this LPS-induced activation of NF-κB. A densitometric evaluation showed that S-flurbiprofen was, with regard to these properties, about 100 times less potent (trace No. 11, 12, 13, 14 against trace No. 10 as control). Trace No. 1 and 8 each showed unstimulated control cells.

Since the nuclear transcription factor NF-κB is, inter alia, responsible for the formation of a series of enzymes with pro-inflammatory and oedema-forming properties, the influence of R-flurbiprofen on the zymosan-induced rat paw oedema was determined (Methods described by:

Meller S.T. and Gebhart G.F.: Intraplantar zymosan as a reliable, quantifiable model of thermal and mechanical hyperalgesia in the rat: European Journal of Pain, 1, 53-52 (1997). Figure 3a-c summarises the results.

Fig. 3a-c: Time-dependent increase of the rat paw volume (measured with a plethysmograph) after intraplanar administration of zymosan. After administration of zymosan /Meller and Gebhart (v. supra)/ into a rear paw of the rat, as indication of an inflammation, it comes to an increase of the paw volume (placebo group, administration of vehicle = phosphate buffer (PP)). On the basis of the inhibiting action of R-flurbiprofen on the NF-κB activation, in the case of dosages in the range between 1 and 27 mg/kg body weight (administration: intraperitoneal), a surprising decrease of the paw volume can be seen. This effect was especially marked between the 2nd and 6th hour after zymosan administration. Dexamethasone (0.5 mg/kg body weight), a known inhibitor of the NF-κB activation, was used as positive control. As expected, S-flurbiprofen also showed a reduction of the paw volume, whereby, however, this effect is explicable not via an inhibition of the NF-κB activation but rather via an inhibition of the synthesis of pro-inflammatory

prostaglandins. S-Flurbiprofen is a known inhibitor of the cyclooxygenases.

Fig. 4: Summary of the effects of 9 mg/kg R-flurbiprofen, 9 mg/kg S-flurbiprofen and 0.5 mg/kg dexamethasone against placebo (V) over 24 hours. The effects after 9 mg/kg R-flurbiprofen were comparable with those after 0.5 mg/kg dexamethasone.

The preparation and chiral separation of the arylpropionic acids and of their derivatives is known. By way of example, reference is made to WO 93-17677 and the literature mentioned therein.

By arylpropionic acid derivatives, there are understood, according to the invention, the derivatives split back into arylpropionic acids in the stomach/intestinal tract (in the case of oral administration) or in the blood, such as alkyl esters with 1 - 6 C-atoms which can possibly contain amino or hydroxyl groups, amides or alkylamides with 1 - 6 C-atoms, as well as pharmaceutically compatible salts, especially alkali metal, alkaline earth metal, ammonium, amino acid salts, preferably lysinate, megluminate, trometamine, arginate or aluminium salts. Such compounds are also known.

The meaning of a prophylactic or therapeutic administration of n.r. R-arylpropionic acid in the acute or chronic treatment of diseases is varied corresponding to the severity of the ailment to be treated. The dose and

frequency of the dosings are also to be differentiated according to the age, body weight and reaction of the individual patients. In general, the daily dose of n.r. R-arylpropionic acid for the described ailments present lies between about 50 mg and about 2000 mg, administered in one or more doses. Preferably, the daily dose lies between about 100 mg and about 500 mg, administered in one or more doses. In the case of the care of the patient, the treatment should be begun with a lower dosing, possibly of 20 mg to 200 mg and increased up to about 1000 mg or higher, depending upon the general reaction of the patient. Furthermore, it is recommended that infants, children, patients over 65 years and those with impaired kidney and liver function first receive a lower dose and titrated based on the individual reaction and the blood level. In some cases, it can be necessary to use a dosing outside this range, which is obvious to the expert. Furthermore, it is to be noted that the treating house physician or clinical specialist knows, in conjunction with the general reaction of the patient, how and when the treatment is to be interrupted, adjusted or discontinued. The espression "an amount which is sufficient for the NF-κB inhibition but is not sufficient in order to initiate disadvantageous reactions (prostaglandin synthesis inhibition)" is included by the given dosage amounts and dosage instructions. Any desired form of administration can be used in order to provide

the patient with an effective dosing of the n.r. R-arylpropionic acid. For example, oral, rectal, transdermal, parenteral (subcutaneous, intramuscular, intravenous), intrathecal, epi- and peridural and similar forms of administration can be used. Possible forms of administration are e.g. tablets, dispersions, suspensions, solutions, plasters and the like.

The pharmaceutical formulations of the present invention include n.r. R-arylpropionic acid as active material or a pharmaceutically compatible derivative thereof and a pharmaceutically compatible carrier material and, if desired, other therapeutic derivatives.

The expression "pharmaceutically compatible derivatives" or "a pharmaceutically compatible derivative thereof" refer to derivatives prepared from pharmaceutically compatible, non-toxic acids or bases, including inorganic acids and bases and organic acids and bases. Since the component of the present invention is acidic, derivatives with pharmaceutically compatible, non-toxic bases, including inorganic and organic bases, can be prepared. Suitable pharmaceutically compatible basic additive derivatives for the components of the present invention include metal salts, prepared from aluminium, calcium, lithium, magnesium, potassium, sodium and zinc, or organic salts prepared from lysine, N,N'-dibenzylethylenediamine, choline, diethanolamine, ethylenediamine, meglumin (N-methylglucamine), tromethamine, arginine and alkylamines with 1 - 6 C-atoms.

The formulations of the present invention include formulations such as suspensions, solutions, elixirs and aerosols. Carrier materials, such as starch, sugar, microcrystalline cellulose, diluents, granulation adjuvants, lubricants, binding agents, solubilisers and the like can be used in the case of the solid oral forms of administration. Solid oral forms of administration (such as powders, capsules and tablets) are preferred to the liquid oral forms of administration. The preferred solid oral forms of administration are tablets. If desired, the tablets can be coated with standardised water or water-free coating agents.

In addition to the usual above-mentioned forms of administration, the component according to the invention can be administered with per se known agents in retarded inflowing and/or rapidly inflowing form. For example, hydrophobing additives to oral forms of administration act delayingly, disintegrating agents and tensides promote dissolving and thus acceleratingly and, as known, both forms can be mixed in granulate form in order to allow a part of the active material to flow in quickly and the rest delayed.

Pharmaceutical formulations of the present invention which are suitable for the oral form of administration can, as separate units, such as capsules, dragees or tablets, in each case contain a pregiven amount of the active material in the form of powder or granulate or as solution or suspension in an aqueous liquid, a non-aqueous liquid,

an oil-in-water emulsion or a liquid water-in-oil emulsion. Such formulations can be prepared according to any pharmaceutical method but all methods comprise a mixing of the active material with a carrier substance which consists of one or more of the necessary components. In general, the formulations are prepared by uniform and thorough mixing of the active material with liquid carrier substances or finely divided solid carrier substances or both and then, if necessary, forming of the product into the desired form of administration.

For example, a tablet can be produced by pressing or forming, if desired with one or more additional components. Pressed tablets can be produced by pressing in an appropriate device when the active material is present in a friable form, such as powder or granulate, optionally mixed with a binding agent, lubricant, inert diluent, dispersing or surface-active agent. Formed tablets can also be produced by shaping of a mixture of the pulverised components, moistened with an inert liquid diluent, in a suitable device and subsequent drying. Preferably, each tablet contains between 50 mg and 1000 mg of the active material and each dragee or capsule contains between about 50 mg and about 600 mg of the active material. Especially preferably, the tablet, dragee or capsule contains one of four dosages, namely, 50 mg, 100 mg, 200 mg or 500 mg of the active material.

7. Use according to claim 1 to 5, characterised in that medicaments are produced in the form of tablets, dragees or other orally usable forms.

8. Use according to claim 1 to 6, characterised in that the active materials are used in rapidly inflowing, retardedly inflowing or combined in rapidly and retardedly inflowing form.

9. Use according to claim 1 to 7, characterised in that they are used for the treatment of rheumatic diseases, pain, asthma, tumours, immune diseases, shock, inflammatory intestinal diseases (Crohn's disease, colitis ulcerosa), radiation damages, arteriosclerosis and Alzheimer's disease, as well as in the case of the treatment of rejection reactions after tissue and organ transplants.

10. Mixtures of 50 - 1000 mg R-enantiomers and 50 - 300 mg S-enantiomers in mixing ratios in which the inhibition of the NF-κB activation of the R-enantiomers is adjusted with the COX inhibition of the S-enantiomers in a medicinal form with regard to action strength and the period of action to the particular indication.

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 31/19

A1

(11) International Publication Number: WO 93/17677

(43) International Publication Date: 16 September 1993 (16.09.93)

(21) International Application Number: PCT/US93/02126

(22) International Filing Date: 8 March 1993 (08.03.93)

(30) Priority data:

848,458	9 March 1992 (09.03.92)	US
024,728	1 March 1993 (01.03.93)	US

(71) Applicant: SEPRACOR, INC. [US/US]; 33 Locke Drive, Marlborough, MA 01752 (US).

(72) Inventors: YOUNG, James, W. ; 1788 Oak Creek Drive, Apt. 411, Palo Alto, CA 94304 (US). GRAY, Nancy, M. ; 261 DeSimone Drive, Marlborough, MA 01752 (US). WECHTER, William, J. ; 12876 Highview Drive, Redlands, CA 92373 (US).

(74) Agents: MISROCK, S., Leslie et al.; Pennie & Edmonds, 1155 Avenue of the Americas, New York, NY 10036 (US).

(81) Designated States: AU, BB, BG, BR, CA, CZ, FI, HU, JP, KR, KZ, LK, MG, MN, MW, NO, NZ, PL, RO, RU, SD, SK, UA, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Published
With international search report.

(54) Title: ANTIPYRETIC AND ANALGESIC METHODS AND COMPOSITIONS CONTAINING OPTICALLY PURE R(-) KETOPROFEN

(57) Abstract

Methods and compositions are disclosed utilizing optically pure R(-) ketoprofen for the treatment of pain including, but not limited to, pain associated with toothaches, headaches, sprains, joint pain and post-surgical pain, for example dental pain and ophthalmic pain, while substantially reducing adverse effects including, but not limited to, gastrointestinal, renal and hepatic toxicities, and leukopenia, which are associated with the administration of racemic ketoprofen. Optically pure R(-) ketoprofen is also useful in treating pyrexia while substantially reducing the adverse effects associated with the administration of racemic ketoprofen.

WO 00/50019 PCT/EP00/00323

Fig. 1

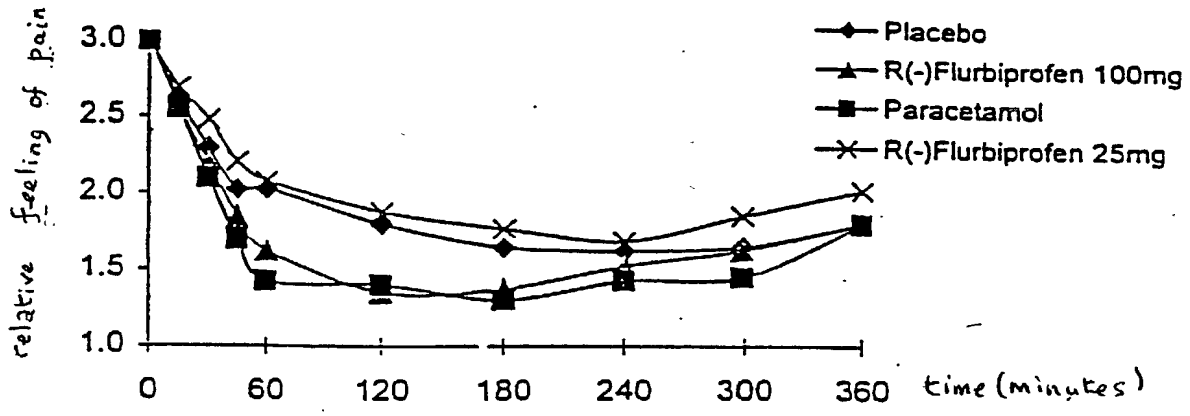
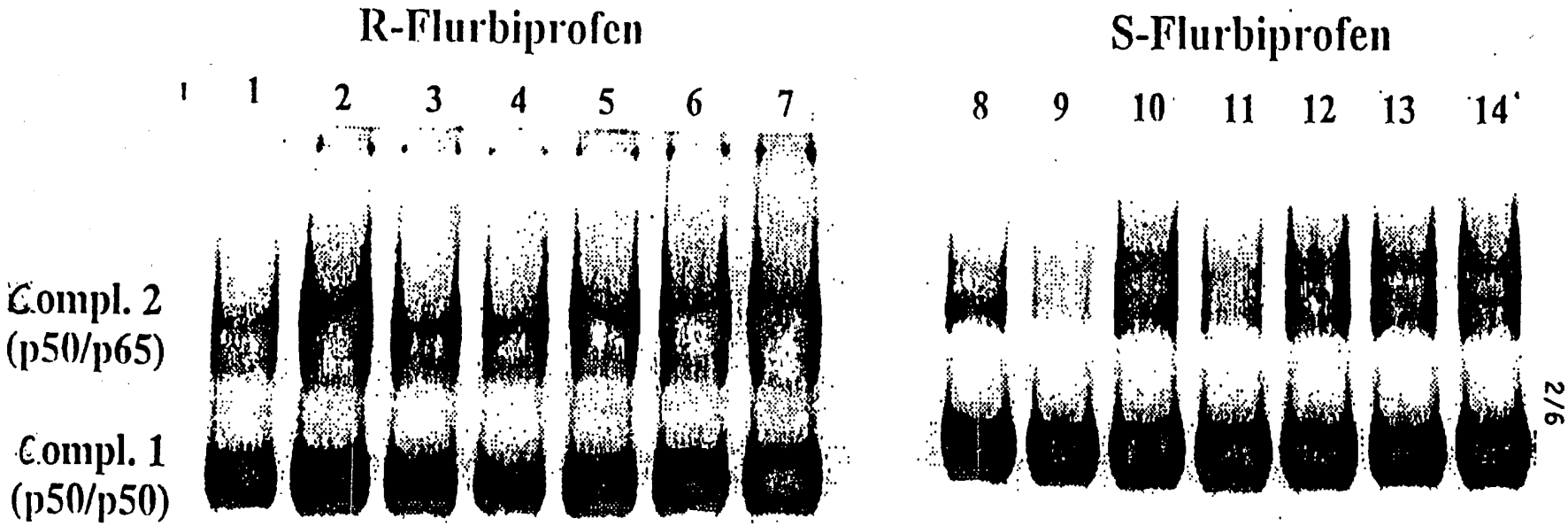


Fig. 2



LPS (1µg/ml)	-	+	+	+	+	+	+	-	-	+	+	+	+	+
R-FLU (µM)	-	-	1000	100	10	1	0,1							
S-FLU (µM)								-	1000	-	1000	100	10	1

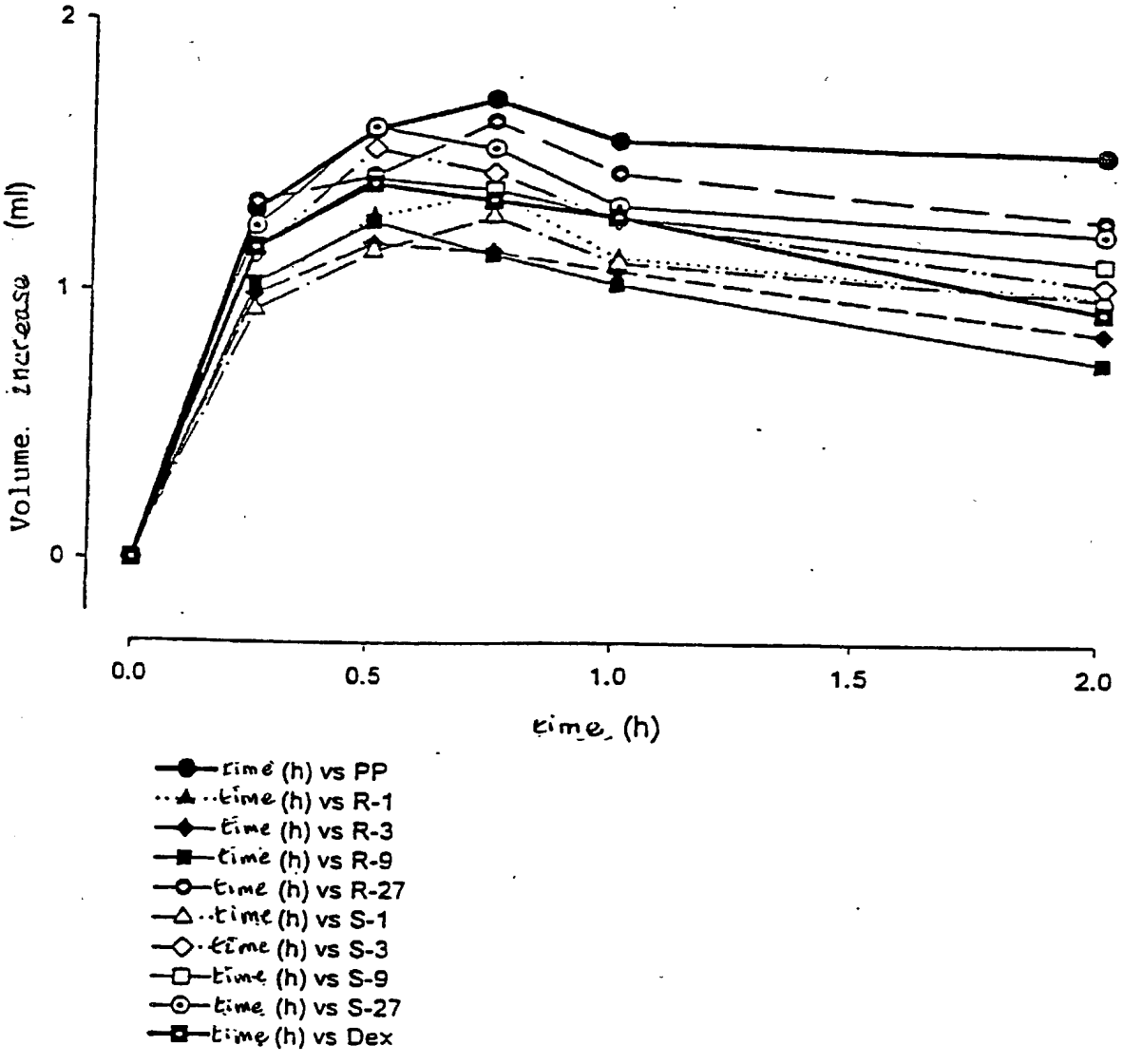

2
1
0
Volume increase (ml)
0.0
0.5
1.0
1.5
2.0
time (h)
time (h) vs PP
time (h) vs R-1
time (h) vs R-3
time (h) vs R-9
time (h) vs R-27
time (h) vs S-1
time (h) vs S-3
time (h) vs S-9
time (h) vs S-27
time (h) vs Dex

Fig. 3a

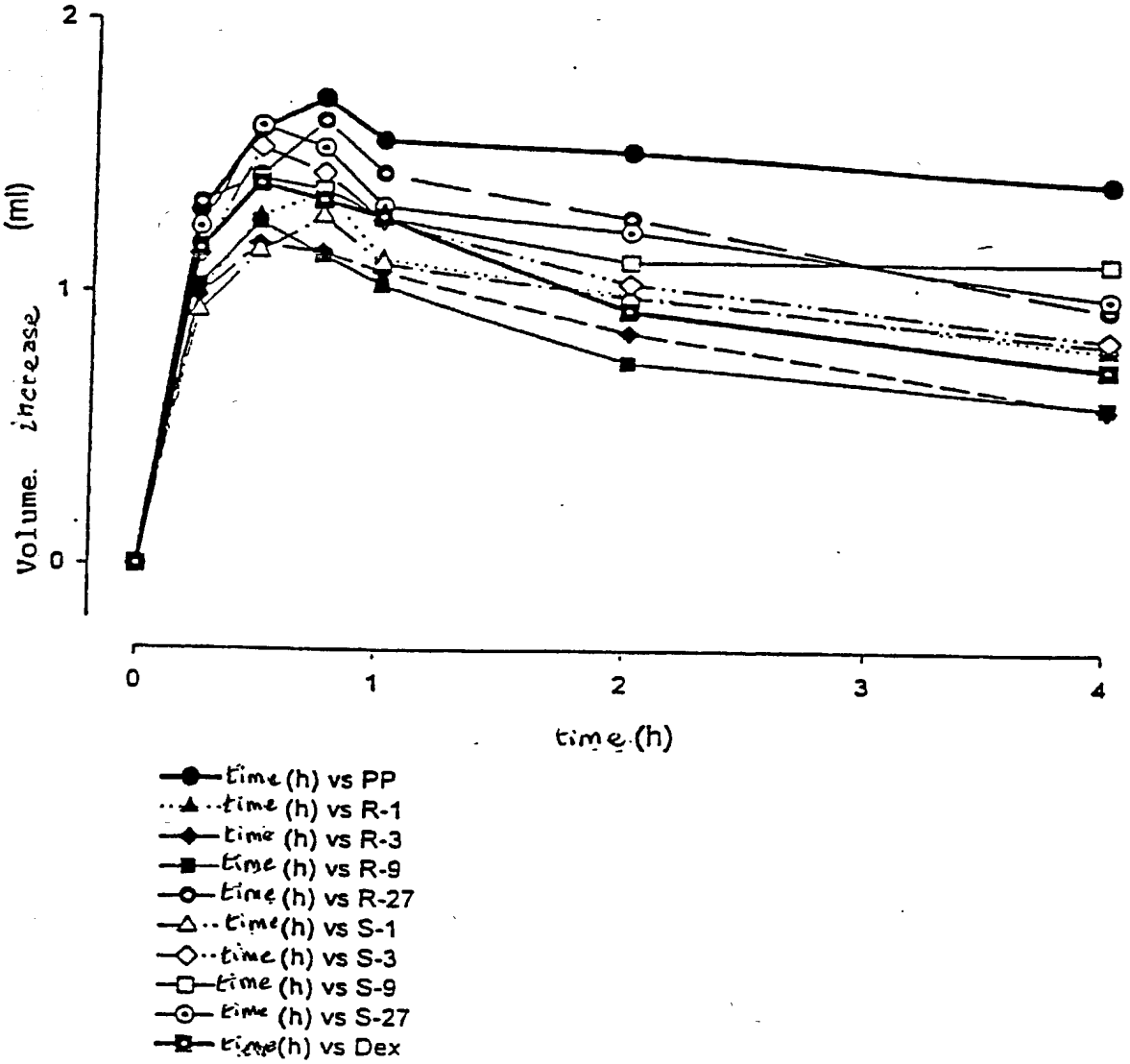

Volume increase (ml)
2
1
0
0
1
2
3
4
time (h)
time (h) vs PP
time (h) vs R-1
time (h) vs R-3
time (h) vs R-9
time (h) vs R-27
time (h) vs S-1
time (h) vs S-3
time (h) vs S-9
time (h) vs S-27
time (h) vs Dex

Fig. 3b

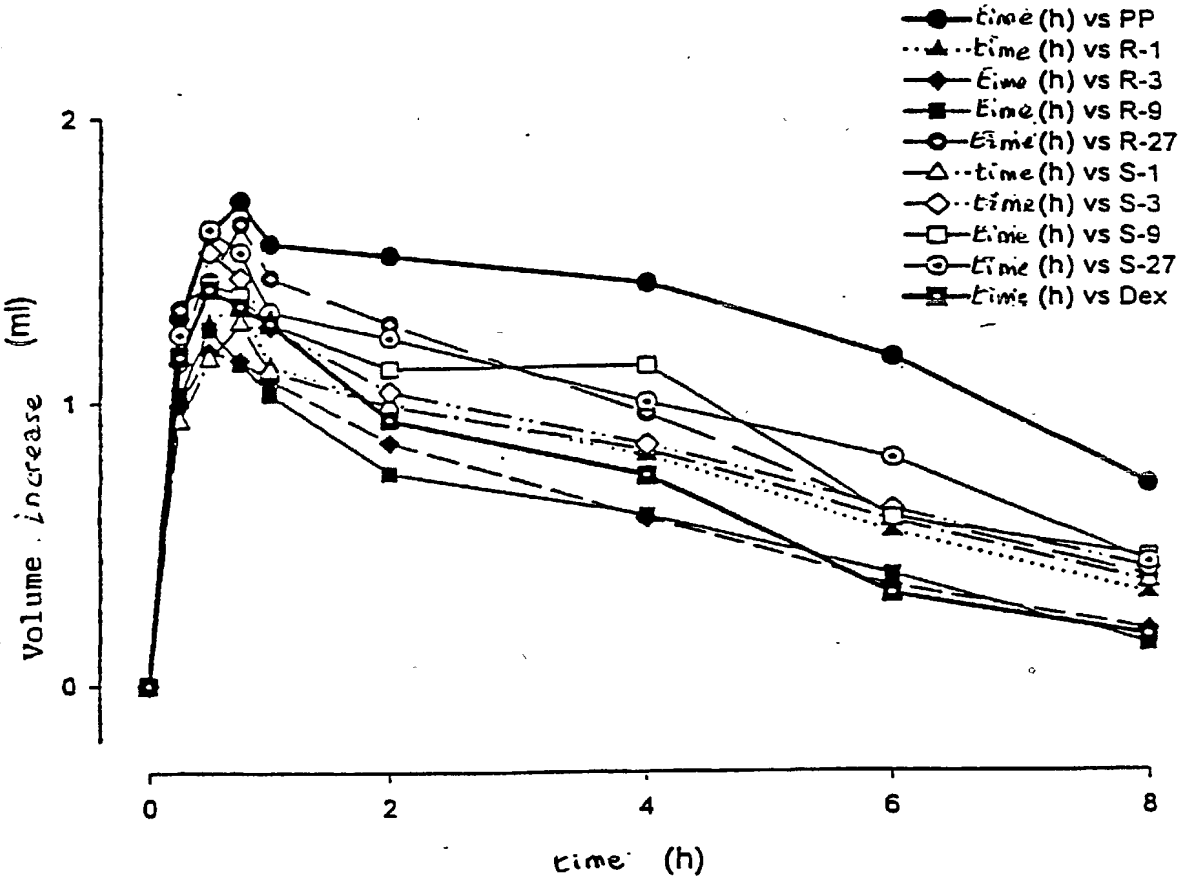
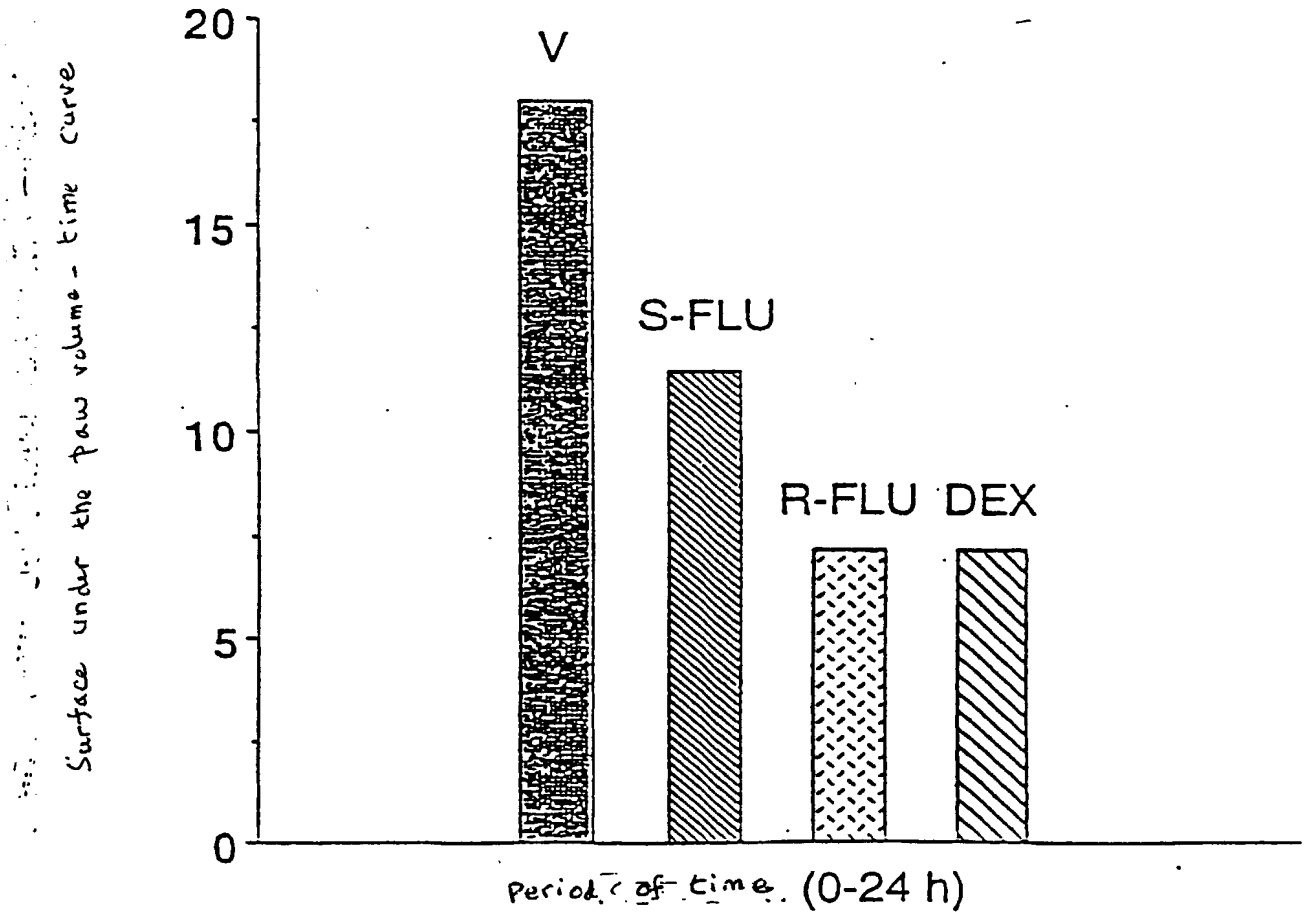

time (h) vs PP
time (h) vs R-1
time (h) vs R-3
time (h) vs R-9
time (h) vs R-27
time (h) vs S-1
time (h) vs S-3
time (h) vs S-9
time (h) vs S-27
time (h) vs Dex
Volume increase (ml)
2
1
0
0
2
4
6
8
time (h)

Fig. 3c

Fig. 4:


20
15
10
5
0
V
S-FLU
R-FLU
DEX
Surface under the paw volume - time curve
Period of time (0-24 h)

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I HEREBY DECLARE:

THAT my residence, post office address, and citizenship are as stated below next to my name;

THAT I believe I am the original, first, and sole inventor (if only one inventor is named below) or an original, first, and joint inventor (if plural inventors are named below or in an attached Declaration) of the subject matter which is claimed and for which a patent is sought on the invention entitled

USE OF R-ARYL PROPIONIC ACIDS FOR PRODUCING MEDICAMENTS TO TREAT DISEASES IN HUMANS AND ANIMALS, WHEREBY SAID DISEASES CAN BE THERAPEUTICALLY INFLUENCED BY INHIBITING THE ACTIVATION OF NF-κB

(Attorney Docket No. 016915-0244)

the specification of which (check one)

___ is attached hereto.

_X_ was filed on January 17, 2000 as United States Application Number or PCT International Application Number PCT/EP00/00323 and was amended on _____ (if applicable).

THAT I do not know and do not believe that the same invention was ever known or used by others in the United States of America, or was patented or described in any printed publication in any country, before I (we) invented it;

THAT I do not know and do not believe that the same invention was patented or described in any printed publication in any country, or in public use or on sale in the United States of America, for more than one year prior to the filing date of this United States application;

THAT I do not know and do not believe that the same invention was first patented or made the subject of an inventor's certificate that issued in any country foreign to the United States of America before the filing date of this United States application if the foreign application was filed by me (us), or by my (our) legal representatives or assigns, more than twelve months (six months for design patents) prior to the filing date of this United States application;

THAT I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment specifically referred to above;

THAT I believe that the above-identified specification contains a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention, and sets forth the best mode contemplated by me of carrying out the invention; and

THAT I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I HEREBY CLAIM foreign priority benefits under Title 35, United States Code §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number	Country	Foreign Filing Date	Priority Claimed?	Certified Copy Attached?
199 07 895.5	Federal Republic of Germany	24 February 1999	YES	

I HEREBY CLAIM the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

U.S. Provisional Application Number	Filing Date

I HEREBY CLAIM the benefit under Title 35, United States Code, §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Application Number	Parent Filing Date	Parent Patent Number

I HEREBY APPOINT the following registered attorneys and agents of the law firm of FOLEY & LARDNER:

STEPHEN A. BENT	Reg. No. 29,768
DAVID A. BLUMENTHAL	Reg. No. 26,257
BETH A. BURROUS	Reg. No. 35,087

3

ALAN I. CANTOR	Reg. No.	28,163
WILLIAM T. ELLIS	Reg. No.	26,874
JOHN J. FELDHAUS	Reg. No.	28,822
MICHAEL D. KAMINSKI	Reg. No.	32,904
LYLE K. KIMMS	Reg. No.	34,079
KENNETH E. KROSIN	Reg. No.	25,735
JOHNNY A. KUMAR	Reg. No.	34,649
JACK LAHR	Reg. No.	19,621
GLENN LAW	Reg. No.	34,371
PETER G. MACK	Reg. No.	26,001
STEPHEN B. MAEBIUS	Reg. No.	35,264
BRIAN J. MC NAMARA	Reg. No.	32,789
SYBIL MELOY	Reg. No.	22,749
RICHARD C. PEET	Reg. No.	35,792
GEORGE E. QUILLIN	Reg. No.	32,792
ANDREW E. RAWLINS	Reg. No.	34,702
BERNHARD D. SAXE	Reg. No.	28,665
CHARLES F. SCHILL	Reg. No.	27,590
RICHARD L. SCHWAAB	Reg. No.	25,479
MICHELE M. SIMKIN	Reg. No.	34,717
HAROLD C. WEGNER	Reg. No.	25,258

(21)

to have full power to prosecute this application and any continuations, divisions, reissues, and reexaminations thereof, to receive the patent, and to transact all business in the United States Patent and Trademark Office connected therewith.

I request that all correspondence be directed to:

Richard L. Schwaab
FOLEY & LARDNER
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5109

Telephone: (202) 672-5414
Facsimile: (202) 672-5399

I UNDERSTAND AND AGREE THAT the foregoing attorneys and agents appointed by me to prosecute this application do not personally represent me or my legal interests, but instead represent the interests of the legal owner(s) of the invention described in this application.

I FURTHER DECLARE THAT all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Atty. Dkt. No. 016915-0244

Name of first inventor	Gerd GEISSLINGER
Residence	Bad Soden, Federal Republic of Germany
Citizenship	Federal Republic of Germany
Post Office Address	Drei-Linden-Strasse 31 D-65812 Bad Soden Federal Republic of Germany
Inventor's signature	
Date	08/24/01
Name of second inventor	Kay BRUNE
Residence	Marloffstein, Federal Republic of Germany
Citizenship	Federal Republic of Germany
Post Office Address	Weiherackerweg 17 D-91080 Marloffstein Federal Republic of Germany
Inventor's signature	
Date	8/20/01